

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P02/193-do/jl	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/11134	International filing date (day/month/year) 08/10/2003	(Earliest) Priority Date (day/month/year) 24/10/2002
Applicant MERCK PATENT GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHYLENE UREA DERIVATIVES AS RAF-KINASE INHIBITORS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11134

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/68 C07D213/75 C07D401/12 C07D413/12 C07D409/12  
 C07D417/12 A61K31/44 A61K31/4427 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/38324 A (LOVELL PETER JOHN ; DEAN DAVID KENNETH (GB); SMITHKLINE BEECHAM PLC (G) 31 May 2001 (2001-05-31)	1-3,7-32
Y	see examples 78-81 and claims 1, 11-15	1-32
X	WO 02/24679 A (SHIMADA MITSUYUKI ; BAYER AG (DE); ZIEGELBAUER KARL B (DE); KORIYAMA Y) 28 March 2002 (2002-03-28)	1-3,7,8, 10-15, 17-23, 26-28, 30-32
	see e.g. example 32-14 and claims 1-4, 6, 7, 9-15	
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

23 July 2004

Date of mailing of the international search report

18. 08. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Traegler-Goeldel, M

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 02/062750 A (SCHERING CORP) 15 August 2002 (2002-08-15)</p> <p>see compound CU on p. 25, compound III on p. 45 and compound 33 page 70; claims 1,2,30,33-37</p>	1-3,7, 10-15, 17-23, 26-28, 30-32
X	<p>EP 0 839 803 A (SS PHARMACEUTICAL CO) 6 May 1998 (1998-05-06)</p> <p>claims 1-3,5,6; examples 1-36</p>	1-3,7, 10-15, 19,20, 22,23, 26-28, 30-32
X	<p>DE 199 47 457 A (AVENTIS PHARMA GMBH) 5 April 2001 (2001-04-05)</p> <p>claims 1-3; examples 5A,5B</p>	1-3,7, 10-15, 19,23, 26-28, 30-32
X	<p>WO 02/12210 A (BERNARDON JEAN MICHEL ;CLARY LAURENCE (FR); GALDERMA RES &amp; DEV (FR) 14 February 2002 (2002-02-14)</p> <p>claims 1,10,15,18; examples 9,10</p>	1-3,7, 10-15, 17,19, 20, 26-28, 30-32
Y	<p>SMITH R A ET AL: "DISCOVERY OF HETEROCYCLIC UREAS AS A NEW CLASS OF RAF KINASE INHIBITORS: IDENTIFICATION OF A SECOND GENERATION LEAD BY A COMBINATORIAL CHEMISTRY APPROACH" BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 20, 2001, pages 2775-2778, XP001118699 ISSN: 0960-894X see lead compound 89</p>	1-32
Y	<p>WO 02/062763 A (RIEDL BERND ;LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK J) 15 August 2002 (2002-08-15) tables 1-6, claims 1-33</p>	1-32

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 057 636 A (PETERSEN HANS JORGEN) 8 November 1977 (1977-11-08)  see the 5 benzylderivatives of table A and examples 37 and 57, its production and pharmacological activity -----	1,2,7, 10-15, 19,23, 26-28,31
X	US 5 441 984 A (HEATH, WILLIAM F., JR. ET AL) 15 August 1995 (1995-08-15)  see examples 6 and 10, its production and activity -----	1,2,7, 10-15, 19,23, 26-28,31
X,P	HOPKINS, THUTAM P. ET AL: "Solid-Phase Synthesis of Trisubstituted Guanidines" JOURNAL OF COMBINATORIAL CHEMISTRY, 4(2), 167-174 CODEN: JCCHFF; ISSN: 1520-4766, 2002, XP002289534 see compound with RN 409080-96-2 and its production -----	1-3, 30-32
X	WO 00/61561 A1 (SHIONOGI BIORESEARCH CORP., USA) 19 October 2000 (2000-10-19)  see inter alia many especially example 26, its production and activity -----	1,2,7, 10-15, 17,18, 21,22, 26-28, 30-32
X	WO 00/61559 A1 (SHIONOGI RESEARCH CORP., USA) 19 October 2000 (2000-10-19)  see e.g. examples 14-16 and scheme on p. 16 -----	1-3,7, 10-15, 17,18, 21,22, 26-28
X	WO 95/18126 A1 (FUJISAWA PHARMACEUTICAL CO., LTD., JAPAN) 6 July 1995 (1995-07-06)  see compound with CAS RN 168971-19-5 -----	2,7, 10-15, 19,20, 21,23, 26-28
X	WO 02/02534 A1 (ASTRAZENECA AB, SWED.; ASTRAZENECA UK LTD.) 10 January 2002 (2002-01-10)  see examples 6, 16 and 31 -----  -/--	2,7,8, 10-15, 17,18, 21,22, 26-28

11 x X  
3 x Y  
1 x P

# INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 01/57008 A1 (BASF AKTIENGESELLSCHAFT, GERMANY) 9 August 2001 (2001-08-09)</p> <p>see e.g. inter alia examples 24 and 26-31 and in combination with scheme II</p> <p>-----</p>	<p>1, 2, 7, 8, 10-15, 17, 18, 20-22, 26-28, 31</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/11134

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-3, 7-32(part)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3, 7-32(part)

Present claims 1 to 3, 7 to 32 relate to an extremely large number of possible compounds, processes for their production, compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

For these two reasons, a meaningful search over the whole breadth of the claims 1 to 3 and 7 to 32 is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the search has been restricted to the compounds of claim 4 to 6 and the claims depending thereon, but only as far as as the specified compounds of claims 4, 5 and 6 are concerned.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11134

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0138324	A	31-05-2001	AU 1529901 A	04-06-2001
			AU 1623601 A	04-06-2001
			BR 0015532 A	25-06-2002
			CA 2395564 A1	31-05-2001
			CZ 20021746 A3	16-10-2002
			EP 1232153 A2	21-08-2002
			EP 1233769 A1	28-08-2002
			WO 0138324 A2	31-05-2001
			HU 0203403 A2	28-02-2003
			JP 2003514860 T	22-04-2003
			JP 2003514906 T	22-04-2003
			NO 20022318 A	15-05-2002
			NZ 518032 A	27-02-2004
			PL 355912 A1	31-05-2004
			TR 200201364 T2	21-10-2002
			WO 0137835 A1	31-05-2001
			ZA 200203987 A	25-11-2003
WO 0224679	A	28-03-2002	JP 2002114777 A	16-04-2002
			AU 8987301 A	02-04-2002
			AU 8987501 A	02-04-2002
			AU 9185201 A	02-04-2002
			BG 107632 A	28-11-2003
			BR 0114073 A	17-06-2003
			CA 2422923 A1	28-03-2002
			CN 1476442 T	18-02-2004
			WO 0224679 A1	28-03-2002
			WO 0224651 A1	28-03-2002
			WO 0224693 A1	28-03-2002
			EP 1326856 A1	16-07-2003
			HU 0303124 A2	29-12-2003
			MA 25836 A1	01-07-2003
			NO 20031307 A	21-03-2003
			SK 3452003 A3	08-01-2004
			US 6562811 B1	13-05-2003
WO 02062750	A	15-08-2002	BR 0206955 A	09-03-2004
			CA 2436659 A1	15-08-2002
			CZ 20032122 A3	15-10-2003
			EP 1368308 A1	10-12-2003
			HU 0304060 A2	28-04-2004
			NO 20033505 A	07-10-2003
			SK 9952003 A3	08-01-2004
			WO 02062750 A1	15-08-2002
			US 2003096844 A1	22-05-2003
			US 2003232859 A1	18-12-2003
EP 0839803	A	06-05-1998	CA 2218300 A1	30-04-1998
			CN 1181377 A , B	13-05-1998
			EP 0839803 A1	06-05-1998
			JP 10182588 A	07-07-1998
			KR 272930 B1	15-11-2000
			TW 438749 B	07-06-2001
			US 5922767 A	13-07-1999
DE 19947457	A	05-04-2001	DE 19947457 A1	05-04-2001
			AU 766365 B2	16-10-2003
			AU 7777800 A	10-05-2001



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11134

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 19947457	A		BR 0014465 A CA 2385859 A1 CN 1373750 T CZ 20021144 A3 EE 200200160 A WO 0125189 A1 EP 1222163 A1 HR 20020264 A2 HU 0203505 A2 JP 2003511363 T NO 20021398 A PL 354322 A1 SK 4382002 A3 TR 200200883 T2 US 2003171351 A1 US 2004102513 A1 US 6531495 B1 ZA 200202521 A	11-06-2002 12-04-2001 09-10-2002 12-06-2002 15-04-2003 12-04-2001 17-07-2002 29-02-2004 28-03-2003 25-03-2003 31-05-2002 12-01-2004 06-08-2002 23-09-2002 11-09-2003 27-05-2004 11-03-2003 30-10-2002
WO 0212210	A	14-02-2002	FR 2812876 A1 AU 8598101 A BR 0113251 A CA 2418895 A1 CN 1468226 T EP 1309575 A1 WO 0212210 A1 JP 2004505958 T US 2004039038 A1	15-02-2002 18-02-2002 24-06-2003 14-02-2002 14-01-2004 14-05-2003 14-02-2002 26-02-2004 26-02-2004
WO 02062763	A	15-08-2002	US 2002165394 A1 WO 02062763 A2	07-11-2002 15-08-2002
US 4057636	A	08-11-1977	GB 1489879 A AT 346357 B AT 936075 A AU 8712775 A BE 836885 A1 CA 1067083 A1 CH 618429 A5 DD 122529 A5 DE 2557438 A1 DE 2560633 C2 DK 572975 A ,B, ES 443725 A1 FI 753520 A ,B, FR 2294703 A1 IE 42141 B1 IT 1062213 B JP 1305959 C JP 51086474 A JP 60028819 B LU 74071 A1 NL 7514852 A ,B, PH 12506 A SE 424637 B SE 7514153 A SU 683615 A3 US RE31244 E	26-10-1977 10-11-1978 15-03-1978 09-06-1977 21-06-1976 27-11-1979 31-07-1980 12-10-1976 24-06-1976 08-09-1988 21-06-1976 16-04-1977 21-06-1976 16-07-1976 04-06-1980 20-09-1983 13-03-1986 29-07-1976 06-07-1985 11-11-1976 22-06-1976 18-04-1979 02-08-1982 21-06-1976 30-08-1979 17-05-1983

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/11134

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
US 4057636	A		YU	316275 A1		28-02-1982
			ZA	7507481 A		26-01-1977
US 5441984	A	15-08-1995	NONE			
WO 0061561	A1	19-10-2000	AU	4080300 A		14-11-2000
			US	6255323 B1		03-07-2001
WO 0061559	A1	19-10-2000	AU	4076500 A		14-11-2000
WO 9518126	A1	06-07-1995	AU	1283195 A		17-07-1995
			JP	9507222 T		22-07-1997
WO 0202534	A1	10-01-2002	AU	1675802 A		14-01-2002
WO 0157008	A1	09-08-2001	AU	3669801 A		14-08-2001
			BG	107062 A		30-04-2003
			BR	0108085 A		18-03-2003
			CA	2398754 A1		09-08-2001
			CN	1422262 T		04-06-2003
			EP	1254123 A1		06-11-2002
			HU	0300359 A2		28-06-2003
			JP	2003521543 T		15-07-2003
			NO	20023713 A		04-10-2002
			SK	12712002 A3		04-02-2003
			US	2003153568 A1		14-08-2003